The § 102(b) Rejection

Claim 1 was rejected under 35 U.S.C. § 102(b) as being anticipated by Kreutter (U.S. 5,627,200). Applicant respectfully traverses this rejection, and submits that the presently claimed pharmaceutical composition is neither taught nor suggested by the cited reference for at least the following reasons.

Kreutter describes methods and pharmaceutical compositions for treating or preventing intestinal motility disorders, depression, prostate disease and dyslipidemia by administering a **β_3-adrenoceptor antagonist or agonist**. Column 1, lines 9-15. Kreutter discloses the synthesis of a number of β_3-adrenoceptor antagonists or agonists, or pharmaceutically acceptable salts or prodrugs thereof, and pharmaceutically acceptable carriers. In particular, for parenteral administration, Kreutter discloses that the **β_3-adrenoceptor antagonist or agonist** active ingredients can be included in a dispersion composition, which can be prepared in sesame or peanut oil, ethanol, water, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, vegetable oils, N-methyl glucamine, polyvinylpyrrolidone and mixtures thereof in oils as well as aqueous solutions of water-soluble pharmaceutically acceptable salts of the compounds. Column 19, lines 60-66. Kreutter further discloses that **β_3-adrenoceptor antagonists or agonists** active ingredients can be combined with other active ingredients known for use in treating atherosclerosis, such as fibrates; in inhibiting cholesterol biosynthesis, such as HMG-CoA reductase inhibitors; and in inhibiting cholesterol absorption, such as beta-sitosterol, and can also be used in combination with anion exchange resins, such as cholestryramine, colestipol or a diaklyaminoalkyl derivatives of

a cross-linked dextran; nicotinyl alcohol, nicotinic acid or a salt thereof; vitamin E, and thyromimetics. Column 26, lines 11-22.

Applicant disagrees with the Examiner's view that Kreutter anticipates Applicants' invention. Kreutter is not anticipatory, *inter alia*, because it does not disclose a feature of Applicant's invention, namely, "wherein said stabilized pharmaceutical composition does not contain a stabilizing effective amount of another stabilizer or a combination of other stabilizers."

Moreover, Kreutter merely lists at least ten dispersion agents, one of which is polyvinylpyrrolidone, and mixtures thereof that can be used in combination with its **β_3-adrenoceptor antagonist or agonist** active ingredients for parenteral administration. Kreutter also merely lists a number of additional categories of active ingredients that may be combined with its **β_3-adrenoceptor antagonist or agonist** active ingredients, one of which includes HMG-CoA reductase inhibitors, such as statins. Kreutter briefly mentions that its **β_3-adrenoceptor antagonist or agonist** active ingredients can also be combined with exchange resins for example cholestyramine, colestipol or a diakylaminoalkyl derivatives of a cross-linked dextran; nicotinyl alcohol, nicotinic acid or a salt thereof; vitamin E; and thyromimetics.

Kreutter, however, does not teach or suggest that any statin, as the only active ingredient, should be selected and combined with an anion exchange resin, such as cholestryramine for treatment of dyslipidemia. One skilled in the art presented with tens of thousands, if not millions of potential **β_3-adrenoceptor antagonist or agonist** active ingredients, at least ten dispersion agents, and a number of additional categories of active ingredients, with no teaching whatsoever to combined statins with polyvinylpyrrolidone

and/or cholestryramine into a stabilized pharmaceutical composition, would not inherently produce an article falling within the scope of any of Applicant's claims.

For the foregoing reasons, Applicant respectfully submits that claim 1 is not anticipated by Kreutter. Applicant respectfully requests withdrawal of the § 102(b) rejection.

The § 103 Rejection

Claims 1-39 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kreutter. In order for a claim to be rejected for obviousness under 35 U.S.C. § 103, the prior art must teach or suggest each element of the claim and suggest combining the elements in the manner contemplated by the claim. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 934 (Fed. Cir. 1990), *cert. denied*, 111 S.Ct. 296 (1990). As pointed out in *In re Fine*, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988), one tests obviousness by what the combined teachings of the references would have suggested to those of ordinary skill in the art.

For reasons already discussed with respect to the § 102 rejection, Kreutter also would not make Applicant's claims 1-39 obvious. Indeed, the Examiner has not provided any teaching, suggestion or motivation that would lead one of skill in the art to modify the teachings of Kreutter to arrive at Applicant's invention. Modifying Kreutter's disclosed method to arrive at Applicant's pharmaceutical composition would require, among other things, that the artisan forgo using a **β_3-adrenoceptor antagonist or agonist** active ingredient. There is no teaching whatsoever in Kreutter to make such a modification.

Claims 1-37 were rejected under § 103(a) as being unpatentable over Tsujita (U.S. 5,627,375). Applicant respectfully traverses this rejection, and submits that the presently claimed pharmaceutical composition is neither taught nor suggested by the cited reference for at least the following reasons.

Tsujita discloses methods and compositions for the treatment and prophylaxis of arteriosclerosis and/or xanthoma using HMG-CoA reductase inhibitors in combination with insulin sensitizers. In fact, Tsujita teaches that by using such a combination, a synergistic effect results, which is significantly better at preventing and/or treating arteriosclerosis and/or xanthoma than either of the components of the combination alone. Column 1, line 50-55. Tsujita also discloses that the active ingredients can be mixed:

> organic vehicles including; sugar derivatives, such as lactose, sucrose, glucose, mannitol and sorbitol; starch derivatives, such as corn starch, potato starch, .alpha.-starch, dextrin and carboxymethylstarch; cellulose derivatives, such as crystalline cellulose, low-substituted hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, calcium carboxymethylcellulose and internally bridged sodium carboxymethylcellulose; gum arabic; dextran; Pullulane; and inorganic vehicles including silicate derivatives, such as light silicic anhydride, synthetic aluminum silicate and magnesium aluminate metasilicate; phosphates, such as calcium phosphate; carbonates, such as calcium carbonate; and sulfates, such as calcium sulfate. Column 5, lines 42-55.

"Examples of binders which may be employed include: polyvinylpyrrolidone; macrogol; and the same compounds as are mentioned above for the vehicles." Column 5, lines 65-67. "Examples of disintegrants which may be employed include: the same compounds as are mentioned above for the vehicles; and chemically modified starches and celluloses, such as sodium crosscarmellose, sodium carboxymethylstarch and bridged polyvinylpyrrolidone." Column 6, lines 1-5.

Tsujita does not render Applicants' invention obvious, *inter alia*, because it does not teach or suggest a feature of Applicant's invention, namely, "wherein said stabilized pharmaceutical composition does not contain a stabilizing effective amount of another stabilizer or a combination of other stabilizers."

Further, Tsujita merely lists at least twenty binders and/or disintegrators, one of which is polyvinylpyrrolidone that can be used in combination with HMG-CoA reductase inhibitors and insulin sensitizers. As the Examiner already noted, Tsujita does not specifically include cholestyramine in its composition. In fact, Tsujita teaches away from the present invention by disclosing that studies have shown that the combination of two lipid regulating agents, pravastatin and cholestryamine, is "insufficient" for controlling hyperlipidemia. Column 1, lines 37-40.

Tsujita also does not teach or suggest that any statin, as the only active ingredient, should be selected and combined with cholestryramine, and/or polyvinylpyrrolidone for treatment of dyslipidemia. One skilled in the art presented with a combination of active ingredients that together create a synergistic effect and a list of at least twenty binders and/or disintegrators, with no teaching whatsoever to combine only the statins with polyvinylpyrrolidone and/or cholestryramine into a stabilized pharmaceutical composition, would not have been motivated to prepare a composition falling within the scope of any of Applicant's claims.

Further, the Examiner has not provided any teaching, suggestion or motivation that would lead one of skill in the art to modify the teachings of Tsujita to arrive at Applicant's invention. Modifying Tsujita's method to arrive at Applicant's pharmaceutical composition would require, among other things, that the artisan forgo

using insulin sensitizers in combination with HMG-CoA reductase inhibitors. There is no teaching whatsoever in Tsujita to make such a modification, nor would it have been obvious to do so given that the combination of a statin (pravastatin) and cholestryramine was already found to be insufficient.

Moreover, both Kreutter and Tsujita fail to teach or suggest that the claimed stabilized pharmaceutical composition should be made and both fail to reveal methods having a reasonable expectation of success of producing a stable pharmaceutical composition of a 7-substituted-3,5-dihydroxyheptanoic acid or heptenoic acid.

For the foregoing reasons, Applicant respectfully submits that claims 1-39 are not obvious in view of Kreutter and claims 1-37 are not obvious in view of Tsujita. Applicant respectfully requests withdrawal of the § 103(a) rejections.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant believes that the application is now in condition for allowance and prompt reconsideration and allowance is earnestly requested.

If the Examiner has any questions or wishes to discuss this application, please telephone the undersigned at the number indicated below.

Respectfully submitted,

Dated: April 11, 2002

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Version with Markings to Show Changes Made

In the specification:

Paragraph [9] has been amended as follows:

Atorvastatin calcium (sold in the U.S. under the trademark **LIPITOR®**) is susceptible to a low pH environment and can degrade to the corresponding lactone in an acidic environment. Mills et al. have stated in U.S. Patent No. 5,686,104 that this and similar compounds in an oral pharmaceutical formulation for the treatment of hypercholesterolemia or hyperlipidemia are stabilized by combination with at least one basic inorganic pharmaceutically acceptable calcium, magnesium, aluminum or lithium salt. Examples of these salts are calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, aluminum magnesium hydroxide or lithium hydroxide. Calcium hydroxide is disclosed as the preferred alkaline earth stabilizing agent. Thus, as in U.S. Patent No. 5,180,[559]589, the stabilizing agents disclosed in U.S. Patent No. 5,686,104 are basic inorganic pharmaceutically acceptable salts.